Acetylenic Chemistry. Part 17 [1]. Acetylenic Amides as Precursors for the Synthesis of 3-Propynylquinazolinones

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Cyclocondensation of acetylenic amides with triethylorthoformate and triethylorthoacetate in boiling glacial acetic acid under nitrogen gave 3-propynylquinazolinones. 2-Ethoxy-2-methyl-3[1,1-dimethylpropynyl]quinazolin-4(1*H*,3*H*)-one (**3b**) and 2-ethoxy-2-methyl-3-[1-cyclohexylpropynyl]quinazolin-4(1*H*,3*H*)-one (**3c**) in refluxing ethanolic sodium hydroxide afforded the corresponding oxazoloquinazolinones.

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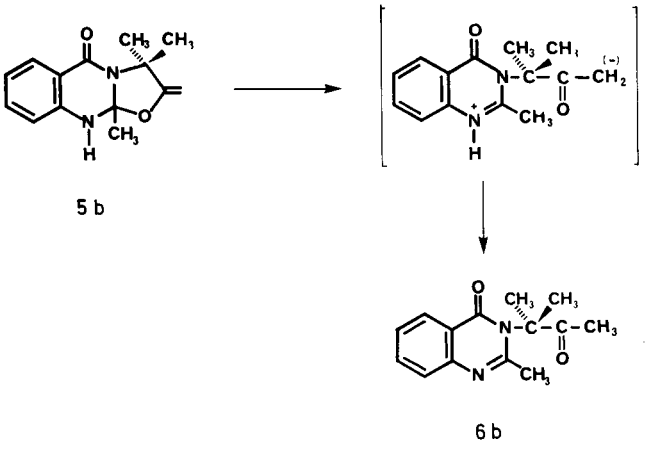
Our continued search for potential biologically active heterocyclic compounds led to the synthesis of some quinazolinones *via* acetylenes [3]. Quinazolinones in general have demonstrated a wide range of interesting biological activities [4,5]. Although the anticonvulsant activity of quinazolinones has not been explored as much as that of benzodiazepines, methaqualone is used clinically as a hypnotic and has also demonstrated potency against major seizure types [6,7].

The acetylenic amides **1a-c** were obtained from the ring opening of isatoic anhydride [3]. Cyclocondensation reactions using orthoesters in the presence of acetic anhydride gave mainly *N*-acetylated products and negligible yields of envisaged 3-propynylquinazolinones. In a blanket of nitrogen using glacial acetic acid, the 3-propynylquinazolinones were obtained in good yields. It was observed that the reaction time, yield and type of product were influenced by substitution on the acetylenic amides. Using triethylorthoformate, the reaction time was increased with a corresponding decrease in yield (unsubstituted > methyl > cyclohexyl). Triethyl orthoacetate however gave some products with ethoxy groups, **3b** and **3c**. Attempted de-ethoxylation of **3b** and **3c** using dilute mineral acids or by prolonged heating did not give the expected product but mainly the corresponding acetylenic amides **1b** and **1c**. However on heating in ethanolic sodium hydroxide, dealkylation with subsequent cyclization afforded the oxazoloquinazolinones **5b** and **5c**. Compound **5b** could only be isolated by stopping the reaction after one hour. However, after 4 hours, **6b** though present in low yield after one hour, was the main product from tlc with a negligible amount of **5b**. This suggests a possible rearrangement reaction shown in Scheme 1.

Scheme 1



Compound **5c** is probably stabilised by the cyclohexyl group. All compounds were characterised by ir, nmr, ms and elemental analysis. The presence of acetylene in the ir absorption of the quinazolinones was evident at about 3200 cm^{-1} (C≡CH) and 2100 cm^{-1} (C≡C). A diagnostic singlet in the aromatic region of the nmr spectra indicating the hydrogen on carbon 2 was observed for compounds **2a-c**. The oxazoloquinazolinones exhibited ir absorptions at 3250 cm^{-1} (N-H), 1710 cm^{-1} (C=O) and 1650 cm^{-1} ($C=CH_2$).

The *trans* and *cis* protons of the exocyclic methylene group were centred as two doublets at 4.20 and 4.80, (J = 3.0 Hz).

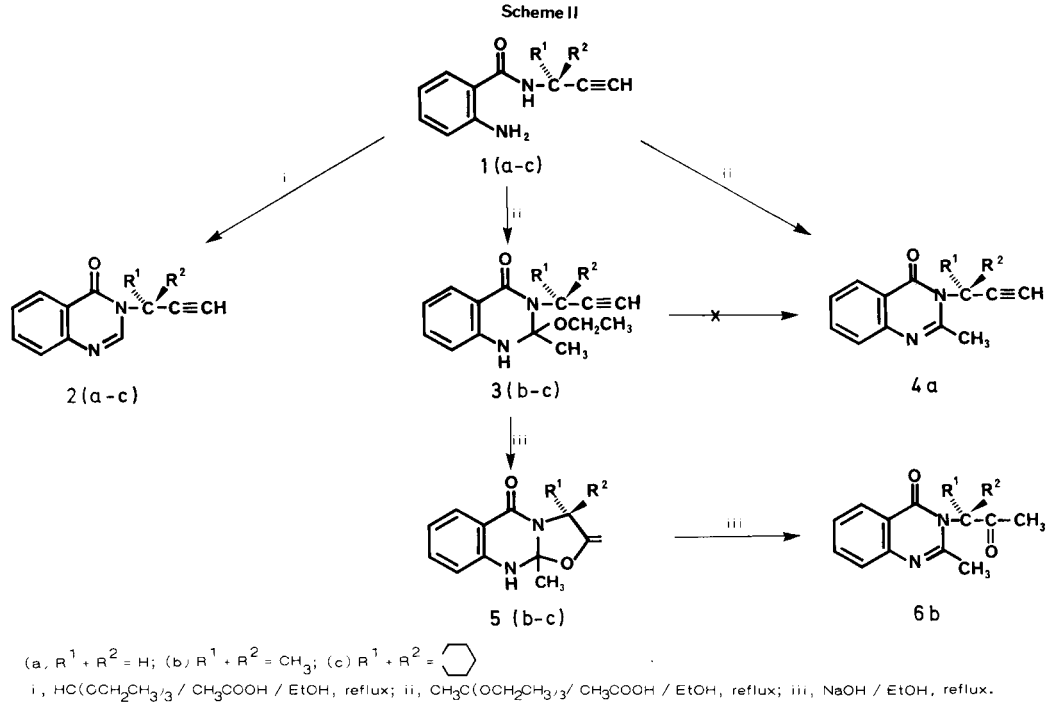
EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and were uncorrected. The ir spectra were recorded on a Pye Unicam SP3-200 ir spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded in deuteriochloroform at 200 MHz with tetramethylsilane as internal standard on a Bruker WM 300 spectrometer. Mass spectra were obtained on a Varian MAT 44S instrument at 70 eV.

Synthesis of Acetylenic Amides.

To isatoic anhydride (0.10 mole) in 20 ml of dimethylformamide was added acetylenic amine (0.15 mole). This was stirred

Scheme II



between 40° and 50° for 2 hours. The reaction mixture was poured into water, 5% sodium hydroxide was added (*p*H = 9) and a solid product collected which was recrystallised from appropriate solvent [3].

General Procedure for the Synthesis of 3-Propynylquinazolinones.

To acetylenic amide (0.006 mole) in 20 of ethanol was added glacial acetic acid (0.006 mole) and triethyl orthoformate or triethyl orthoacetate (0.006 mole). The reaction mixture was stirred and heated to reflux under nitrogen until tlc indicated complete disappearance of the acetylenic amide (2-16 hours) [8]. The resulting solution was concentrated *in vacuo*, basified with 5% sodium hydroxide (*p*H = 8) and extracted into dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to give solid products which were recrystallised from appropriate solvents. Column chromatography was carried out where necessary for purification of the solid products.

3-Propynylquinazolin-4(3*H*)-one (**2a**).

The condensation of *o*-amino-*N*-propynylbenzamide (**1a**) 1.0 g (0.006 mole) with triethyl orthoformate 1.10 ml (0.006 mole) after 4 hours gave from methanol 3-propynylquinazolin-4(3*H*)-one (**2a**) as colorless needles, 0.93 g (88%), mp 115-116°; ir (potassium bromide): 3210 (C≡CH), 2110 (C≡C), 1660 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.51 (t, J = 2.5 Hz, 1H, H-3'), 4.83 (d, J = 4.1 Hz, 2H, H-1'), 7.52 (ddd, J = 1.9, 6.3, 7.8 Hz, 1H, H-6), 7.74 (s, 1H, H-2), 7.76 (dd, J = 1.8, 7.9 Hz, 1H, H-8), 8.3 (m, 2H, H-5, H-7); ^{13}C nmr (deuteriochloroform): δ 35.2 (C-1'), 75.2 (C-3'), 77.8 (C-2'), 122.1 (C-4a), 127.1 (C-8), 127.8 (C-6), 127.9 (C-5), 134.8 (C-7), 145.4 (C-2), 148.3 (C-8a), 160.7 (C-4); ms: 184 (M^+, 100), 155 (30), 142 (8), 129 (42), 116 (6), 102 (34), 90 (4), 76 (34), 63 (20), 51 (20).

Anal. Calcd. for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.99; H,, 4.44; N, 15.27.

3-[1,1-Dimethylpropynyl]quinazolin-4(3*H*)-one (**2b**).

The condensation of *o*-amino-*N*-(1,1-dimethylpropynyl)benzamide (**1b**) 1.21 g (0.006 mole) with triethyl orthoformate 1.10 ml (0.006 mole) after 6 hours gave from chloroform/petroleum ether 40-60° 3-[1,1-dimethylpropynyl]quinazolin-4(3*H*)-one (**2b**) as colorless needles 0.55 g (43%), mp 97-99°; ir (potassium bromide): 3240 (C≡CH), 2980 (C-H), 2100 (C≡C), 1660 (C=O) cm^{-1}; ^1H nmr (deuteriochlorofrom); δ 2.08 (s, 6H, 2 x CH_3), 2.93 (s, 1H, H-3'), 7.44-7.58 (ddd, J = 1.9, 6.3, 8.2 Hz, 1H, H-6), 7.64-7.80 (m, 2H, H-7, H-8), 8.30 (dd, J = 1.1, 7.8 Hz, 1H, H-5), 8.96 (s, 1H, H-2); ^{13}C nmr (deuteriochloroform): δ 28.5 (2 x CH_3), 58.4 (C-2'), 77.9 (C-3'), 84.7 (C-1'), 127.1 (C-4a, 8), 127.5 (C-5, 6), 134.6 (C-7), 145.1 (C-2), 148.0 (C-8a), 161.7 (C-4); ms: 212 (M^+, 58), 197 (14), 183 (8), 169 (10), 146 (100), 131 (8), 118 (28), 102 (16), 90 (26), 69 (26).

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.28; H, 5.70; N, 13.14.

3-[1-Cyclohexylpropynyl]quinazolin-4(3*H*)-one (**2c**).

The condensation of *o*-amino-*N*-cyclohexylpropynylbenzamide (**1c**) 1.45 g (0.006 mole) with triethyl orthoformate 1.10 ml (0.006 mole) after 16 hours gave from petroleum ether (40-60°) 3-[1-cyclohexylpropynyl]quinazolin-4(3*H*)-one (**2c**), as colorless needles 0.45 g (30%), mp 96-97°; ir (potassium bromide): 3200 (C≡CH), 2910 (C-H), 2100 (C≡C), 1660 (C=O); cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.52-2.90 (m, 10H, cyclohexyl), 2.97 (s, 1H, H-3'), 7.48 (dd, J = 1.7, 7.5 Hz, 1H, H-6), 7.68-7.82 (m, 2H, H-7, H-8), 8.28 (dd, J = 1.5, 7.5 Hz, 1H, H-5), 8.92 (s, 1H, H-2); ^{13}C nmr (deuteriochloroform); δ 23.7 (C-3'', 5''), 24.7 (C-4''), 34.5 (C-2'', 6''), 64.0 (C-2'), 80.2 (C-3'), 82.0 (C-1'), 123.4 (C-4a), 127.2 (C-8), 127.4 (C-6), 127.5 (C-5), 134.6 (C-7), 145.1 (C-2), 147.6 (C-8a), 161.8 (C-4); ms: 252 (M^+, 28), 251 (M^+-1, 36), 237 (12), 224 (98), 211 (8), 198 (100), 147 (92), 129 (14), 118 (14), 106 (44), 91 (74), 78 (32), 65 (16), 51 (16).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.17; H, 6.39; N, 11.10. Found: C, 76.07; H, 6.37; N, 11.01.

2-Methyl-3-propynylquinazolin-4-(3*H*)-one (**4a**).

The condensation of *o*-amino-*N*-propynylbenzamide (**1a**) 1.0 g (0.006 mole) with triethyl orthoacetate 1.10 ml (0.006 mole) after 2 hours gave as colorless needles from dichlorometane/petroleum ether (40-60°) 2-methyl-3-propynylquinazolin-4-(3*H*)-one (**4a**), 0.99 g (83%), mp 91-93°; ir (potassium bromide): 3220 (C≡CH), 2960 (C-H), 2110 (C≡C), 1680 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.35 (t, J = 2.5 Hz, 1H, H-3'), 2.75 (s, 1H, C-2-CH_3), 4.91 (d, J = 2.5 Hz, 2H, H-2'), 7.44 (ddd, J = 1.4, 7.1, 8.3 Hz, 1H, H-6), 7.62 (dd, J = 1.4, 8.3 Hz, 1H, H-8), 7.73 (ddd, J = 1.6, 7.0, 8.2 Hz, 1H, H-7), 8.25 (dd, J = 1.6, 8.1 Hz, 1H, H-5); ^{13}C nmr deuteriochloroform): δ 22.8 (C-2-CH_3), 33.1 (C-1'), 72.7 (C-3'), 77.6 (C-2'), 120.5 (C-4a), 126.8 (C-8), 127.0 (C-6), 127.2 (C-5), 134.8 (C-7), 147.5 (C-8a), 154.0 (C-2), 161.6 (C-4); ms: 198 (M^+, 100), 197 (M^+-1, 88), 183 (22), 169 (36), 156 (6), 143 (10), 129 (14), 117 (8), 102 (14), 90 (12), 76 (14).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.33; H, 5.08; N, 14.01.

2-Ethoxy-2-methyl-3-[1,1-dimethylpropynyl]quinazolin-4(1*H*,-3*H*)-one (**3b**).

The condensation of *o*-amino-*N*-(1,1-dimethylpropynyl)benzamide (**1b**) 1.21 g (0.006 mole) with triethyl orthoacetate 1.10 ml (0.006 mole) after 2 hours gave as colorless plates from pentane 2-ethoxy-2-methyl-3-[1,1-dimethylpropynyl]quinazolin-4(1*H*,-3*H*)-one (**3b**), 0.98 g (60%), mp 97-98°; ir (potassium bromide): 3260 (NH), 3200 (C≡CH), 2980 (C-H), 2100 (C≡C), 1630 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.74 (s, 6H, 2 x CH_3), 1.97 (s, 3H, C-2-CH_3), 2.36 (s, 1H, ≡CH), 4.36 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 6.67 (dd, J = 1.2, 7.8 Hz, 1H, H-8), 7.17 (ddd, J = 1.3, 7.4, 7.9 Hz, 1H, H-6), 7.34 (ddd, J = 1.7, 7.4, 7.8 Hz, 1H, H-7), 8.05 (brs, 1H, NH), 8.12 (dd, J = 1.7, 7.9 Hz, 1H, H-5); ^{13}C nmr (deuteriochloroform): δ 14.20 (C-2-CH_3), 17.1 (OCH$_2$CH_3), 29.1 (2 x CH_3), 47.9 (OCH_2CH$_3$), 62.4 (C-2'), 69.1 (C-3'), 88.1 (C-1'), 122.5 (C-8), 124.1 (C-6), 126.4 (C-4a), 131.2 (C-5), 131.9 (C-7), 146.8 (C-8a), 164.1 (C-2), 165.9 (C-4); ms: 272 (M^+, 20), 244 (20), 229 (12), 202 (16), 162 (100), 144 (44), 120 (36), 105 (12), 92 (14), 77 (12), 65 (18).

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.69; H, 7.32; N, 10.12.

2-Ethoxy-2-methyl-3-[1-cyclohexylpropynyl]quinazolin-4(1*H*,-3*H*)-one (**3c**).

The reaction of *o*-amino-*N*-cyclohexylpropynylbenzamide (**1c**) 1.45 g (0.006 mole) with triethyl orthoacetate 1.10 ml (0.006 mole) after 2 hours gave as colorless plates from petroleum ether (40-60°) 2-ethoxy-2-methyl-3-[cyclohexylpropynyl]quinazolin-4(1*H*,3*H*)-one (**3c**) 1.57 g (84%), mp 88-89°; ir (potassium bromide): 3300 (NH), 3200 (C≡CH), 2860-2980 (C-H), 2100 (C≡C), 1630 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.31-2.14 (m, 10H, cyclohexyl), 1.38 (t, J = 7.2 Hz, OCH$_2$CH_3), 1.86 (s, 3H, C-2-CH_3), 2.42 (s, 1H, H-3'), 4.31 (q, J = 7.2 Hz, 2H, OCH_2CH$_3$), 6.66 (dd, J = 1.1, 7.8 Hz, 1H, H-8), 7.18 (ddd, J = 1.3, 7.4, 7.7 Hz, 1H, H-6), 7.35 (ddd, J = 1.7, 7.4, 7.8 Hz, 1H, H-7), 7.85 (brs, 1H, NH), 8.12 (dd, J = 1.7, 7.8 Hz, 1H, H-5); ^{13}C nmr (deuteriochloroform): δ 14.2 (C-2-CH_2), 17.1 (OCH$_2$CH_3), 22.7 (C-3'', 5''), 26.4 (C-4''), 37.0 (C-2', 6'), 52.2 (OCH_2CH$_3$), 62.3 (C-2'), 71.3 (C-3'), 86.3 (C-1'), 122.5 (C-8), 124.1 (C-6), 126.5 (C-4a), 131.3 (C-5), 131.9 (C-7), 146.8 (C-8a), 164.2 (C-2), 165.8 (C-4); ms: 312 (M^+, 26), 284 (48), 258 (16), 238 (36), 225 (20), 212 (54), 189 (12), 162 (100), 144 (58), 120 (42), 105 (12), 92 (18), 77 (14), 65 (20).

Anal. Calcd. for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.03; H, 7.73; N, 8.87.

Preparation of Oxazoloquinazolinones **5b** and **5c**.

To a stirred solution of 2-ethoxy-2-methyl-3-[1,1-dimethylpropynyl]quinazolin-4(1*H*,3*H*)-one (**3b**) or 2-ethoxy-2-methyl-2-[1-cyclohexylpropynyl]quinazolin-4(1*H*,3*H*)-one (**3c**) in 20 ml of ethanol, sodium hydroxide was added and heated gradually to reflux under nitrogen. The reaction was stopped, excess solvent removed, 20 ml of water added and adjusted to *p*H 8 with 5% hydrochloric acid. The aqueous solution was extracted with dichloromethane, dried (anhydrous sodium sulfate), and evaporated to give oily crystalline solid. Column chromatography was used to purify the compounds.

2-Methylene-2b-methyl-3,3-dimethyloxazolo[2,3-*b*]quinazolin-5-(4*H*,10*H*)-one (**5b**).

The reaction of 2-ethoxy-2-methyl-3-[1,1-dimethylpropynyl]-quinazolin-4-(1*H*,3*H*)-one (**3b**) 1.0 g (0.004 mole) with sodium hydroxide 0.16 g (0.004 mole) in ethanol after 1 hour gave two products. Column chromatography (chloroform) of the solid afforded 2-methylene-2b-methyl-3,3-dimethyloxoazolo[2,3-*b*]quinazolin-5-(4*H*,10*H*)-one (**5b**), 0.19 g (21%) as the first eluate which from pentane were colorless crystals mp 72-73°; ir (potassium bromide): 3250 (NH), 2900-3100 (C-H), 1700 (C=O), 1640 (C=CH$_2$) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.48 (s, 6H, 2 x CH_3), 2.22 (s, 3H, CH_3), 4.30 (d, J = 3.0 Hz, 1H, =CH_{trans}), 4.79 (d, J = 3.0 Hz, 1H, =CH_{cis}), 7.12 (ddd, J = 1.2, 7.3, 7.9 Hz, 1H, H-7), 7.49 (ddd, J = 1.7, 7.2, 7.4 Hz, 1H, H-8), 7.90 (dd, J = 1.7, 7.9 Hz, 1H, H-9), 8.72 (dd, J = 1.1, 8.5 Hz, 1H, H-6), 11.96 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 25.3 (C-CH_3), 30.0 (C-2 x CH_3), 69.4 (C-3), 83.3 (C-=CH_2), 112.4 (C-5a), 120.2 (C-7), 122.6 (C-9), 129.4 (C-6), 133.3 (C-8), 140.5 (C-9a), 160.5 (C-5), 166.2 (C-2), 169.6 (C-2b); ms: 245 (M^+ + 1, 18), 244 (M^+, 100), 229 (46), 216 (10), 202 (7), 187 (14), 173 (29), 161 (78), 146 (42), 119 (84), 118 (63), 91 (35), 69 (16). Found M^+ 244.1209; requires 244.1212.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.48; H, 6.87; N, 10.53.

2-Methyl-3-(1,1-dimethylacetonyl)quinazolin-4(3*H*)-one (**6b**).

The second eluate gave as colorless crystals from dichloromethane/petroleum ether 40-60°, 2-methyl-3-(1,1-dimethylacetonyl)quinazolin-4(3*H*)-one (**6b**), 0.45 g (50%), mp 108-110°; ir (potassium bromide) 2900-3000 (C-H), 1710, 1680 (C=O), 1630 (C=N), 1600 (C=C) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.76 (s, 6H, 2 x CH_3), 2.16 (s, 3H, H-3'), 2.78 (s, 3H, C-2-CH_3), 7.45 (ddd, J = 1.3, 6.9, 7.1 Hz, 1H, H-7), 7.62 (dd, J = 0.6, 7.1 Hz, 1H, H-8), 7.73 (ddd, J = 1.6, 6.7, 7.1 Hz, 1H, H-6), 8.14-8.19 (dd, J = 0.6, 8.0 Hz, 1H, H-5); ^{13}C nmr: δ 23.8 (C-3'), 24.7 (C-2 x CH_3), 26.7 (C-2-CH_3), 69.1 (C-1'), 120.7 (C-4a), 126.6 (C-8), 127.1 (C-6), 127.2 (C-5), 135.1 (C-7), 147.1 (C-8a), 154.0 (C-2), 164.2 (C-4), 202.6 (C-2'); ms: 245 (M^+ + 1, 5), 244 (M^+, 27), 229 (4), 202 (83), 160 (100), 143 (95), 132 (4), 118 (21), 117 (24), 102 (12), 91 (29), 76 (34), 65 (13).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.38; H, 6.64; N, 11.42.

2-Methylene-2b-methyl-3-cyclohexyloxazolo[2,3-*b*]quinazolin-5(4*H*,10*H*)-one (**5c**).

The reaction of 2-ethoxy-2-methyl-3-(1-cyclohexylpropynyl)-quinazolin-4(1*H*,3*H*)-one (**3c**) 1.0 g (0.003 mole) with sodium hydroxide 0.38 g (0.01 mole) in ethanol after 3 hours gave oily crystalline solid. Purification by column chromatography (chloro-

form) gave 2-methylene-2b-methyl-3-cyclohexyloxazolo[2,3-*b*]-quinazolin-5(4*H*,10*H*)-one (**5c**) which from methanol-water were colorless plates, 0.42 g (46%), mp 111-112° ir (potassium bromide): 3250 (NH), 2900-3100 (C-H), 1710 (C=O), 1650 (C=CH_2); ^{1}H nmr (deuteriochloroform): δ 1.56-1.89 (m, 10H, cyclohexyl), 2.26 (s, 3H, CH_3), 4.28 (d, J = 3.0 Hz, 1H, $=CH_{trans}$), 4.80 (d, J = 3.0 Hz, 1H, $=CH_{cis}$), 7.13 (ddd, J = 1.2, 7.4, 8.0 Hz, 1H, H-7), 7.75 (ddd, J = 1.7, 7.2, 7.4 Hz, 1H, H-8), 7.92 (dd, J = 1.7, 7.9 Hz, 1H, H-9), 8.78 (dd, J = 1.1, 8.4 Hz, 1H, H-6), 12.28 (brs, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 22.8 (C-3', 5'), 25.5 (C-CH_3), 25.6 (C-4'), 39.5 (C-2', 6'), 72.3 (C-3), 83.5 (C-=CH_2), 112.3 (C-5a), 120.0 (C-7), 122.6 (C-9), 129.4 (C-6), 133.3 (C-8), 140.7 (C-9a), 160.3 (C-5), 166.4 (C-2), 169.5 (C-2b); ms: 285 (M^++1, 18), 284 (M^+, 94), 269 (54), 242 (20), 241 (22), 213 (28), 161 (100), 118 (64), 109 (21), 81 (38), 67 (26), 54 (8).

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 72.02; H, 7.21; N, 9.87.

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